Original Article

Associations between persistent postoperative anaemia and mortality 1 year after valvular heart surgery: a retrospective cohort study*

Hee Won Choi, Hyun-Soo Zhang, Jae-Kwang Shim, Jin Sun Cho, Seo Hee Ko and Young Lan Kwak

Summary

Introduction Peri-operative anaemia is a common problem in patients undergoing cardiac surgery. Postoperative anaemia is not well understood relative to pre-operative anaemia; limited data exist on haemoglobin recovery and mortality after discharge, especially in the era of restrictive transfusion practice. We aimed to investigate the associations of pre-operative and persistent postoperative anaemia with 1-year mortality in patients undergoing valvular heart surgery.

Methods We identified patients who had undergone valvular heart surgery and allocated them to one of four groups based on their pre-operative (haemoglobin ≥ 130 $g.l^{-1}$ and < 130 $g.l^{-1}$ in men and ≥ 120 $g.l^{-1}$ and < 120 $g.l^{-1}$ in women) and postoperative (measured 2 months after surgery; haemoglobin ≥ 100 $g.l^{-1}$ and < 100 $g.l^{-1}$ in both men and women) anaemia status. The four groups were: pre- and postoperative non-anaemia (non-anaemia–non-anaemia); pre-operative anaemia–postoperative non-anaemia (anaemia–non-anaemia); pre- and postoperative anaemia (anaemia–anaemia); and pre-operative non-anaemia–postoperative anaemia (non-anaemia–anaemia). The primary outcome was 1-year mortality.

Results Data from 2486 patients were included. Pre-operative anaemia was diagnosed in 1107 patients (44.5%) and 279 (11.9%) met the diagnostic criteria for persistent anaemia 2 months postoperatively. The overall 1-year mortality rate was 3.3%. The highest rate was observed in the anaemia–anaemia group (17.8%), followed by the non-anaemia–anaemia (13.1%), anaemia–non-anaemia (2.9%) and non-anaemia–non-anaemia (0.5%) groups. Multivariable Cox regression analysis showed that the non-anaemia–anaemia group had the highest risk of 1-year mortality (adjusted hazard ratio 14.44, 95%CI 4.88–42.69), followed by the anaemia–anaemia group (adjusted hazard ratio 10.94, 95%CI 4.41–27.16).

Discussion Our study highlights the high prevalence of persistent anaemia following valvular heart surgery. Persistent anaemia 2 months postoperatively is associated with an increased risk of 1-year mortality.

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Plain Language Summary may be found on PubMed and in the Supporting Information.

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Introduction

Peri-operative anaemia is prevalent in patients undergoing cardiac surgery, with a reported incidence of 20–54% [1, 2]. Pre-operative anaemia has been associated with an increased risk of mortality and morbidity in this patient population [3, 4]. Accordingly, treatment of pre-operative anaemia is a key component of patient blood management in cardiac surgery [5]. In contrast, the natural course of postoperative anaemia is not as well understood, with limited data on haemoglobin recovery following successful recovery from surgery and discharge from hospital. Cardiac surgery requiring cardiopulmonary bypass (CPB) is accompanied by haemodilution, coagulopathy, bleeding and systemic inflammation, contributing to ineffective restorative erythropoiesis, all of which increase the risk of persistent anaemia [1, 6, 7]. Moreover, restrictive transfusion practices leave many patients with anaemia at discharge, imposing an additional burden on haemoglobin recovery [8, 9].

It is biologically plausible that persistent postoperative anaemia is associated with worse long-term outcomes not only by interfering with tissue oxygen delivery but also reflecting a heightened inflammatory state, accounting for the close observed association with persistent anaemia and suppressed erythropoiesis [6]. To date, most studies addressing postoperative anaemia have focused on the immediate and/or early postoperative period [10–12], leaving the long-term trajectory of peri-operative anaemia and its association with patient outcomes largely unexplored.

In this study, we aimed to explore the association of pre- and postoperative anaemia status with 1-year mortality in patients undergoing valvular heart surgery, with particular emphasis on the prognostic role of persistent postoperative anaemia in patients who did and did not have anaemia before surgery.

Methods

The study protocol was approved by the Institutional Review Board and Hospital Research Ethics Committee of Severance Hospital at the Yonsei University Health System, and the requirement for informed consent was waived.

We included patients who underwent valvular heart surgery between 1 January 2016 and 31 July 2023 at the Severance Cardiovascular Hospital of the Yonsei University Health System in Seoul, Republic of Korea. Patients who underwent valvular heart surgery and simultaneous coronary artery bypass grafting or replacement of the ascending aorta were also included. Only patients aged > 18 y were included in the analysis. We did not study: patients who underwent only pulmonary valve replacement surgery (as this group typically comprises younger individuals with congenital heart disease); patients who died within 2 months of surgery; and patients with missing haemoglobin values at 2 months postoperatively.

Patient data up to 31 January 2024 were retrieved retrospectively from the electronic medical records. We collected pre-operative data, including patient characteristics, medical history, medications and the predicted 30-day mortality estimated by the European System for Cardiac Operative Risk Evaluation (EuroSCORE-2). Pre-operative laboratory tests included: haemoglobin concentration; red blood cell distribution width; platelet count; plasma creatinine; plasma albumin; and plasma C-reactive protein concentrations. Monocyte-to-lymphocyte ratio was used as an indicator of inflammation [13]. Operative data included the type and urgency of surgery; duration of CPB; and duration of aortic cross-clamp. Requirement for intra- and postoperative allogeneic red blood cell transfusion and volume of re-infused cell salvage (as a surrogate for intra-operative blood loss) were collected. Postoperative transfusion was assessed over two timeframes: at discharge; and within a 1-year period after discharge. In general, a red blood cell transfusion occurred when the haemoglobin concentration was < 70 $g.l^{-1}$ during CPB; < 80 $g.l^{-1}$ after CPB; and postoperatively at the discretion of the attending physician.

We also obtained information on ICU and duration of hospital stay. Adverse postoperative events before discharge were included, specifically myocardial infarction (defined using the fourth Universal Definition of Myocardial Infarction [14]); cardiac arrest; new-onset atrial fibrillation; acute kidney injury (defined by the Kidney Disease Improving Global Outcomes guidelines [15] as a 26.4 $mmol.l^{-1}$ increase in serum creatinine level within 48 h or 50% increase in serum creatinine level from baseline within 7 days); continuous renal replacement therapy; sternal wound infection; stroke; delirium (assessed daily using the Confusion Assessment Method for the ICU during the ICU stay [16]); pneumonia; respiratory failure (requiring pulmonary rehabilitation or tracheostomy); mechanical ventilator support for over 48 h; tracheal re-intubation; and cardiac re-operation. We defined our composite measure of postoperative complications as the occurrence of at least one adverse event.

We used the World Health Organization definition of pre-operative anaemia (haemoglobin < 130 $g.l^{-1}$ for men and < 120 $g.l^{-1}$ for women) based on the last haemoglobin measurement before the index surgery [17]. We recorded the nadir haemoglobin during surgery and the last

recorded haemoglobin before exiting the operating theatre. After surgery, haemoglobin levels were measured at least once per day until discharge. After discharge, patients were encouraged to attend the hospital at 2 weeks and 2 months postoperatively for follow-up. Postoperative anaemia was defined as a haemoglobin < 100 $g.l^{-1}$ at 2 months postoperatively. This threshold has been used in previous studies involving both cardiac [18–20] and non-cardiac surgical patient populations [21–23], in which significant associations between postoperative anaemia and clinical outcomes were reported [24, 25]. Patients were classified into four groups: pre- and postoperative non-anaemia (non-anaemia–non-anaemia); pre- and postoperative anaemia (anaemia–anaemia); pre-operative anaemia and postoperative non-anaemia (anaemia–non-anaemia); and pre-operative non-anaemia and postoperative anaemia (non-anaemia–anaemia).

The primary outcome was mortality at 1 year. The survival status of patients lost to follow up was verified using nationwide census data from the Ministry of the Interior and Safety of Korea. We performed time-to-event analysis, with survival time calculated from the date of surgery to the date of all-cause death or last follow-up, whichever occurred first. We explored the non-anaemia–anaemia group secondarily to identify the risk factors associated with the development of postoperative anaemia in patients without pre-operative anaemia.

We compared baseline patient characteristics and peri-operative clinical data between the four groups using the Kruskal–Wallis test for continuous variables and the χ^2 or Fisher's exact test for categorical variables depending on count. Tukey's correction was used to adjust for multiple pairwise comparisons.

The pre- and postoperative anaemia status variable, along with other possible peri-operative variables, were considered as possible risk factors for 1-year mortality. Variables with $p < 0.05$ in univariable Cox regression analyses were selected for inclusion in the multivariable model. All potential risk factors were evaluated for collinearity before inclusion in the multivariable analysis. To avoid multicollinearity, we did not include variables that were components of the EuroSCORE-2 index, such as: age; sex; comorbidities; left ventricular ejection fraction; type of surgery; and emergency surgery. The univariable analyses, Akaike information criterion-based stepwise variable selection [26] and least absolute shrinkage and selection operator selection [27] results were assessed comprehensively alongside clinical and epidemiological judgement to finalise the multivariable models of 1-year mortality. Further detailed information regarding this multivariable modelling process is provided in online Supporting Information Appendix S1 and conceptually illustrated in online Supporting Information Figures S1 and S2.

Multivariable Cox model hazard ratios with corresponding 95%CIs and p-values were derived. We evaluated the discriminative ability of the multivariable model using Harrell's C-index [26] and the adjusted survival curves of the four groups were plotted based on this multivariable model. The proportional hazards assumption was checked for the multivariable model using the cox.zph function of the R package `survival´ [28].

We calculated the E-value of the hazard ratio point estimate and its corresponding lower 95%CI to assess the effect of potentially unmeasured confounders in a sensitivity analysis [29]. The E-value represents the minimum strength of association that an unmeasured confounder would need to have with both exposure and outcome to fully nullify the observed association. In addition, the possible interaction or effect moderation between the pre- and postoperative anaemia status variables was evaluated. For secondary analysis, we used multivariable logistic regression to identify the risk factors for new postoperative anaemia among patients without pre-operative anaemia. Model performance was evaluated using the area under the receiver operating characteristic curve (AUROC).

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA) for descriptive and univariable analyses and R version 4.3.3 (R Foundation for Statistical Computing, Vienna, Austria) for variable selection and multivariable modelling. All statistical tests were two-sided, and statistical significance was set at $p < 0.05$.

Results

In total, 3065 patients were screened; 579 patients were not studied based on the exclusion criteria, and the remaining 2486 were included in the analyses (Fig. 1). Pre-operatively, 1107 (44.5%) patients had anaemia and 297 (11.9%) had anaemia at 2 months postoperatively. Among the included patients, 236 (9.5%) were allocated to the anaemia–anaemia group; 1318 (53.0%) to the non-anaemia–non-anaemia group; 871 (35.0%) to the anaemia–non-anaemia group; and 61 (2.5%) to the non-anaemia–anaemia group (Fig. 1).

Patient characteristics and comorbidities varied significantly among the four groups (Table 1; full version available in online Supporting Information Table S1). Patients in the anaemia–anaemia group were older, had more comorbidities and had a higher EuroSCORE-2 than the other groups. These patients required more allogeneic

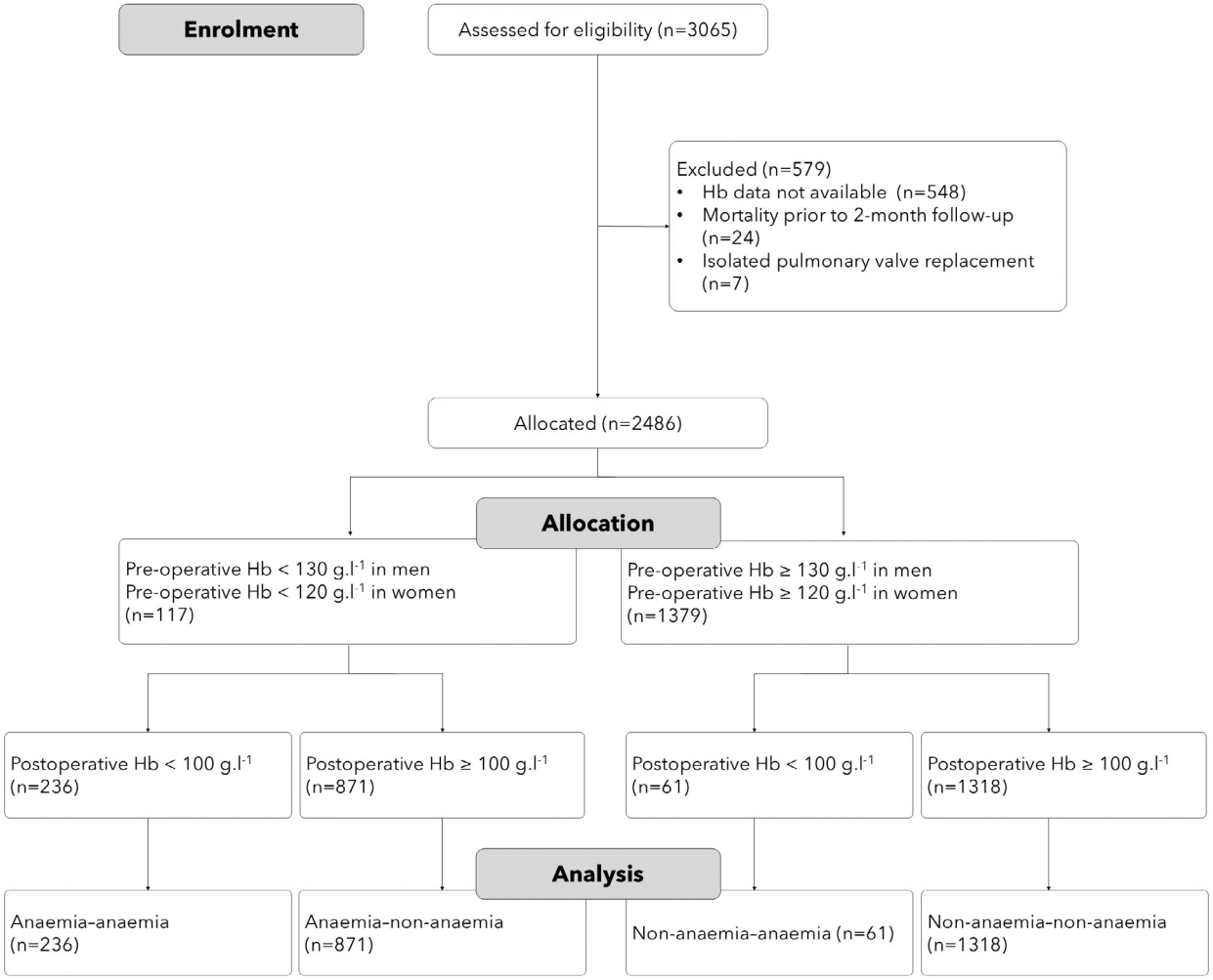


Figure 1 Study flow diagram. Hb, haemoglobin.

red blood cell transfusions throughout the assessment period. Patients in the non-anaemia–anaemia group had longer CPB and aortic cross-clamp durations than those of the other groups. All laboratory findings, including haematological and inflammatory indices, showed significant differences among the four groups (online Supporting Information Table S2).

The overall 1-year mortality rate was 3.3% (81/2046), with significant between-group differences ($p < 0.001$) (Table 2). The highest mortality rate was observed in the anaemia–anaemia group (42/236, 17.8%), followed by the non-anaemia–anaemia (8/61, 13.1%), anaemia–non-anaemia (25/871, 2.9%) and non-anaemia–non-anaemia (6/1318, 0.5%) groups. The duration of hospital stay was significantly longer in the anaemia–anaemia group than in the other groups ($p < 0.001$). The incidence of composite postoperative complications was the highest in the anaemia–anaemia group, followed by the non-anaemia–anaemia group; both incidence rates were significantly higher than those in the other groups ($p < 0.001$).

The unadjusted Kaplan–Meier and multivariable Cox model-adjusted 1-year survival curves for the four groups are shown in Figure 2. Survival probabilities varied significantly among the four groups (log-rank test, $p < 0.001$). Following univariable Cox regression (online Supporting Information Table S3) and a predefined variable selection process, five risk factors were included in the multivariable Cox model: pre- and postoperative anaemia groups; EuroSCORE-2; monocyte–leucocyte ratio; requirement for postoperative allogenic red blood cell transfusion; and composite of postoperative complications (Table 3). After adjusting for the other four variables, the pre- and postoperative anaemia group stratification remained significantly associated with 1-year mortality ($p < 0.001$). Compared with the non-anaemia–non-anaemia group (reference), all other groups showed significantly

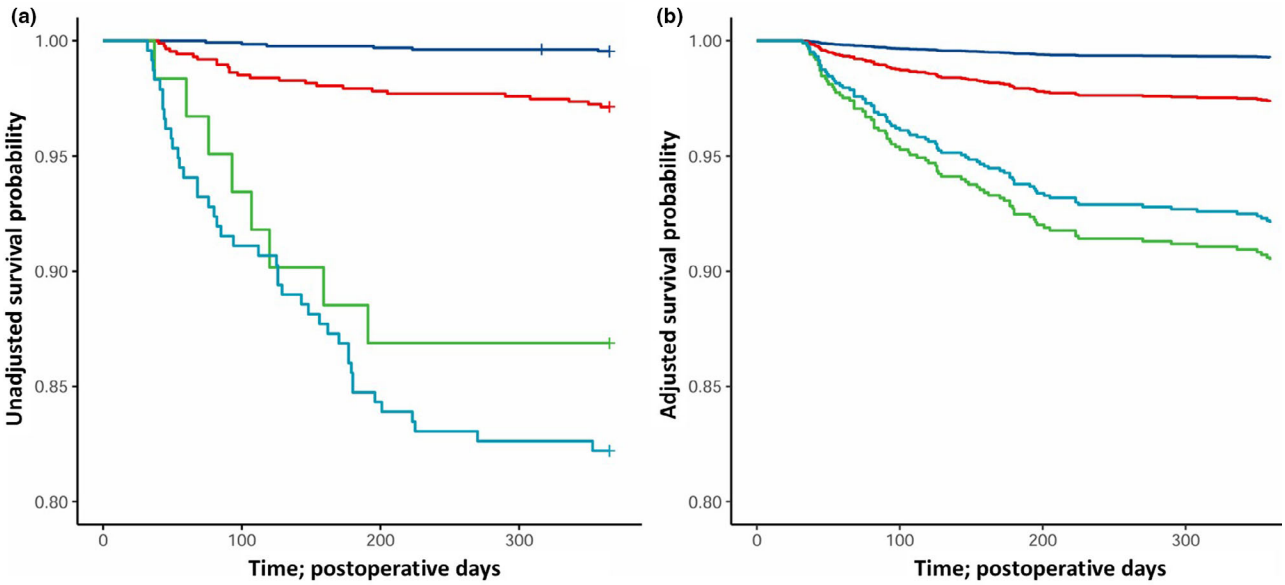
Table 1 Baseline characteristics and peri-operative clinical data of patients according to the four pre- and postoperative anaemia groups. Values are median (IQR [range]) or number (proportion).

	Total n = 2486	Non-anaemia–non-anaemia n = 1318	Anaemia–anaemia n = 236	Anaemia–non-anaemia n = 871	Non-anaemia–anaemia n = 61	p-value
Age; y	66 (57–73 [18–90])	63 (54–70 [18–87])	71 (65–77 [19–87])	67 (59–74 [18–86])	67 (60–75 [32–90])	< 0.001
Sex; female	1238 (49.8%)	636 (48.3%)	119 (50.4%)	443 (50.9%)	40 (65.6%)	0.037
BMI; $kg.m^{-2}$	23.6 (21.4–25.9 [13.5–39.5])	24.2 (22.1–26.4 [14.9–37.8])	22.7 (20.5–25.3 [14.3–38.7])	22.9 (20.9–25.3 [13.5–39.5])	23.4 (21.2–24.9 [15.0–29.3])	< 0.001
LVEF; %	64 (57–70 [15–89])	65 (58–70 [15–88])	62 (53–69 [20–84])	65 (58–71 [18–88])	62 (57–69 [22–89])	< 0.001
EuroSCORE-2	2.6 (1.2–5.1 [0–64.5])	1.8 (0.9–4.0 [0.0–21.0])	6.0 (2.9–10.0 [0.5–64.5])	3.3 (1.5–6.0 [0.0–52.8])	3.4 (2.3–7.0 [0.7–16.0])	< 0.001
Type of surgery						< 0.001
Aortic valve	707 (28.4%)	379 (28.8%)	62 (26.3%)	252 (28.9%)	14 (23.0%)	
Mitral valve	884 (35.6%)	492 (37.3%)	71 (30.1%)	306 (35.1%)	15 (24.6%)	
Double valve	330 (13.3%)	148 (11.2%)	37 (15.7%)	135 (15.5%)	10 (16.4%)	
Valve + CABG	169 (6.8%)	65 (4.9%)	26 (11.0%)	71 (8.2%)	7 (11.5%)	
Valve + aorta	254 (10.2%)	162 (12.3%)	19 (8.1%)	66 (7.6%)	7 (11.5%)	
Tricuspid valve	142 (5.7%)	72 (5.5%)	21 (8.9%)	41 (4.7%)	8 (13.1%)	
Emergency	27 (1.1%)	8 (0.6%)	7 (3.0%)	12 (1.4%)	0	0.008
Aortic cross-clamping time; min	65 (45–90 [15–782])	63 (44–86 [15–353])	74 (45–103 [15–782])	66 (45–92 [20–292])	84 (65–113 [21–325])	< 0.001
Cardiopulmonary bypass time; min	95 (70–126 [26–810])	90 (68–120 [26–430])	109 (74–147 [31–810])	95 (70–130 [36–500])	120 (95–149 [49–541])	< 0.001
Transfusion data						
Cell salvage volume; ml	490 (460–690 [70–4910])	500 (460–700 [163–2000])	484 (460–690 [130–4910])	480 (450–680 [70–2250])	608 (460–740 [250–3790])	< 0.001
Intra-operative transfusion	956 (38.5%)	258 (19.6%)	181 (76.7%)	486 (55.8%)	31 (50.8%)	< 0.001
Postoperative transfusion	1174 (47.2%)	400 (30.3%)	199 (84.3%)	532 (61.1%)	43 (70.5%)	< 0.001
Within discharge	1154 (46.4%)	391 (29.7%)	197 (83.5%)	529 (60.7%)	37 (60.7%)	< 0.001
After discharge	113 (4.5%)	17 (1.3%)	44 (18.6%)	41 (4.7%)	11 (18.0%)	< 0.001
Haemoglobin; $g.l^{-1}$						
Pre-operative	126 (111–138 [64–197])	137 (130–145 [64–197])	102 (91–112 [64–197])	111 (99–118 [64–197])	133 (125–148 [64–197])	< 0.001
Postoperative 2 months	121 (109–131 [51–170])	128 (118–137 [100–170])	92 (85–96 [54–99])	117 (109–125 [100–162])	94 (90–96 [51–99])	< 0.001

Missing data: LVEF, 5 (0.1%); cell salvage volume, 24 (1.0%).
CABG, coronary artery bypass graft; EuroSCORE-2, European System for Cardiac Operative Risk Evaluation; LVEF, left ventricular ejection fraction.

Table 2 Postoperative outcomes of patients according to the four pre- and postoperative anaemia groups. Values are number (proportion) or median (IQR [range]).

	Total n = 2486	Non-anaemia–non-anaemia n = 1318	Anaemia–anaemia n = 236	Anaemia–non-anaemia n = 871	Non-anaemia–anaemia n = 61	p-value
1-year mortality	81 (3.3%)	6 (0.5%)	42 (17.8%)	25 (2.9%)	8 (13.1%)	< 0.001
Duration of ICU stay; days	3 (2–3 [1–160])	3 (2–3 [7–13])	4 (3–8 [2–95])	3 (3–4 [2–66])	3 (3–6 [1–160])	< 0.001
Duration of hospital stay; days	11 (9–15 [6–386])	10 (8–12 [6–73])	22 (13–49 [7–255])	12 (9–17 [6–386])	14 (11–25 [8–199])	< 0.001
Myocardial infarction	3 (0.1%)	1 (0.1%)	2 (0.8%)	0	0	0.009
Cardiac arrest	17 (0.7%)	4 (0.3%)	5 (2.1%)	6 (0.7%)	2 (3.3%)	0.001
New-onset atrial fibrillation	321 (12.9%)	171 (13.0%)	34 (14.4%)	108 (12.4%)	8 (13.1%)	0.878
Acute kidney injury	576 (23.2%)	184 (14.0%)	125 (53.0%)	241 (27.7%)	26 (42.6%)	< 0.001
Continuous renal replacement therapy	105 (4.2%)	2 (0.2%)	55 (23.3%)	37 (4.2%)	11 (18.0%)	< 0.001
Sternal wound infection	52 (2.1%)	13 (1.0%)	15 (6.4%)	14 (1.6%)	10 (16.4%)	< 0.001
Stroke	62 (2.5%)	17 (1.3%)	20 (8.5%)	22 (2.5%)	3 (4.9%)	< 0.001
Delirium	155 (6.2%)	27 (2.0%)	60 (25.4%)	55 (6.3%)	13 (21.3%)	< 0.001
Pneumonia	114 (4.6%)	14 (1.1%)	53 (22.5%)	38 (4.4%)	9 (14.8%)	< 0.001
Respiratory failure	51 (2.1%)	2 (0.2%)	25 (10.6%)	16 (1.8%)	8 (13.1%)	< 0.001
Prolonged ventilator care > 48 h	104 (4.2%)	12 (0.9%)	43 (18.2%)	42 (4.8%)	7 (11.5%)	< 0.001
Tracheal reintubation	93 (3.7%)	10 (0.8%)	44 (18.6%)	28 (3.2%)	11 (18.0%)	< 0.001
Cardiac reoperation	138 (5.6%)	51 (3.9%)	29 (12.3%)	42 (4.8%)	16 (26.2%)	< 0.001
Composite of postoperative complications	995 (40.0%)	402 (30.5%)	177 (75.0%)	378 (43.4%)	38 (62.3%)	< 0.001



Patient at risk

Pre-and postoperative anaemia groups	0 month	4 months	8 months	12 months
Non-anaemia–non-anaemia	1318	1315	1313	1312
Anaemia–anaemia	236	214	196	194
Anaemia–non-anaemia	871	857	851	846
Non-anaemia–anaemia	61	55	53	53

Patient at risk

Pre- and postoperative anaemia groups	0 month	4 months	8 months	12 month
Non-anaemia–non-anaemia	1316	1314	1311	1310
Anaemia–anaemia	236	215	196	195
Anaemia–non-anaemia	871	857	851	847
Non-anaemia–anaemia	61	57	53	53

Figure 2 Survival curves using the (a) Kaplan–Meier and (b) multivariable Cox model methods for 1-year mortality according to group assignment. Blue, non-anaemia–non-anaemia; sky blue, anaemia–anaemia; red, anaemia–non-anaemia; green, non-anaemia–anaemia.

increased risk of 1-year mortality; the non-anaemia–anaemia group had the highest risk (adjusted hazard ratio 14.44, 95%CI 4.88–42.69, $p < 0.001$), followed by the anaemia–anaemia group (adjusted hazard ratio 10.94, 95% CI 4.41–27.16, $p < 0.001$) and the anaemia–non-anaemia group (adjusted hazard ratio 3.33, 95%CI 1.33–8.30, $p = 0.010$). The risks of mortality did not differ significantly between the anaemia–anaemia and non-anaemia–anaemia groups ($p = 0.486$). The concordance index of the final prognostic model was 0.882 (95%CI 0.843–0.921). The proportional hazards assumption was satisfied for all five variables included in the final prognostic model, especially for the pre- and postoperative anaemia groups' variable, with a Schoenfeld residual-based test (p-value of 0.554).

A sensitivity analysis was conducted using the E-value methodology (Table 3). For the 1-year mortality, the adjusted hazard ratio for the non-anaemia–anaemia group was 14.44 (95%CI 4.88–42.69), corresponding to an E-value of 28.37 for the point estimate and 9.23 for the lower CI. The E-values for the anaemia–anaemia and anaemia–non-anaemia groups were 21.37 and 6.12 for point estimates and 8.29 and 1.99 for lower CIs, respectively. These relatively high E-values and the fact that the E-values of 9.23 and 8.29 for the lower CI exceeded the point estimate hazard ratios of all other covariates in the model (1.05, 3.12, 2.45 and 3.77, respectively) indicated the robustness of the observed associations and suggested that they are unlikely to be explained by unmeasured confounders.

In the interaction analysis, we found a statistically significant interaction between the pre- and postoperative anaemia status variable and 1-year mortality (interaction term, $p = 0.008$) upon adjustments for other confounders. The magnitude of this moderating effect was evaluated by stratifying the survival analyses (online Supporting Information Table S4). Stratification by pre-operative anaemia status revealed that, in patients who did not have pre-operative anaemia, persistent anaemia 2 months postoperatively had a pronounced effect on 1-year mortality (adjusted hazard ratio 16.59). This strong association might have attenuated the relative contributions of other covariates in the model, as none of the additional predictors reached statistical significance in this subgroup. In contrast, for patients with pre-operative anaemia, the impact of persistent anaemia 2 months postoperatively on mortality

Table 3 Multivariable Cox proportional hazards model* of 1-year mortality after valvular heart surgery and corresponding E-values.

Variables	Hazard ratio	95%CI	p-value	E-value for point estimate	E-value for lower 95%CI
Group			< 0.001		
Non-anaemia–non-anaemia	Ref			Ref	
Anaemia–anaemia	10.94	4.41–27.16	< 0.001	21.37	8.29
Anaemia–non-anaemia	3.33	1.33–8.30	0.010	6.12	1.99
Non-anaemia–anaemia	14.44	4.88–42.69	< 0.001	28.37	9.23
EuroSCORE-2	1.05	1.03–1.08	< 0.001		
Monocyte-to-lymphocyte ratio	3.12	1.89–5.16	< 0.001		
Requirement for postoperative allogeneic red blood cell transfusion	2.45	1.12–5.37	0.025		
Sustained postoperative complication	3.77	1.87–7.59	< 0.001		

EuroSCORE-2, European System for Cardiac Operative Risk Evaluation.
*Multivariable model concordance index (95%CI): 0.882 (0.843–0.921).

was relatively low (adjusted hazard ratio 3.20), while retaining statistical significance.

Among patients without pre-operative anaemia, the risk factors for new, persistent postoperative anaemia included: elevated pre-operative red blood cell distribution width; longer CPB time; requirement for intra-operative allogenic red blood cell transfusion; and development of postoperative complications (Table 4). The AUROC of this multivariable logistic regression model was 0.795 (95%CI 0.732–0.858). Univariable logistic regression results are provided in online Supporting Information Table S5.

Discussion

In this retrospective, single-centre, observational study, persistent postoperative anaemia assessed 2 months after valvular heart surgery was observed in 11.9% of patients and showed an independent association with 1-year mortality, irrespective of the pre-operative anaemia status. Mortality increased by 14.5-fold and 11-fold in patients who developed postoperative anaemia (non-anaemia–anaemia) and those who had anaemia before surgery (anaemia–anaemia), respectively, compared with patients who did not have anaemia at any time point (non-anaemia–non-anaemia). These findings underscore the prognostic importance of monitoring postoperative haemoglobin recovery, as persistent postoperative anaemia is associated with, and may be a risk factor for, poor long-term outcomes following valvular heart surgery.

Postoperative anaemia after cardiac surgery is common, with a reported incidence of 29%–94%, based on the definition and patient population [9]. In our study, the incidence was 11.9% using a haemoglobin threshold of 100 $g.l^{-1}$ and 57.9% using the World Health Organization criteria measured at 2 months postoperatively. These findings are comparable with those of a previous study reporting 19% incidence with haemoglobin <90 $g.l^{-1}$ and 44% according to the World Health Organization criteria at 50 days after coronary artery bypass grafting [13]. While pre-operative anaemia is a well-established risk factor for poor outcomes in cardiac surgery [3, 4, 30], the long-term impact of postoperative anaemia is not well studied. Most research has focused on early postoperative anaemia, typically defined as occurring within 2–10 days or before discharge; this phenomenon is correlated with adverse outcomes, particularly when the haemoglobin falls below 70–89 $g.l^{-1}$ [10, 11]. However, evidence of the effects of persistent postoperative anaemia and the clinical implications of the changing anaemia status over time remain limited [10–12].

In this study, both pre- and postoperative anaemia and newly developed persistent postoperative anaemia were associated significantly with increased 1-year mortality after valvular heart surgery, with large E-values supporting the robustness of these findings against potentially unmeasured confounders. Postoperative anaemia was four times more common in patients with pre-operative anaemia than in those without and was associated with the highest 1-year mortality in the anaemia–anaemia group. This aligns with the findings by Opera et al. in which increased mortality was reported in patients with both pre- and postoperative anaemia (adjusted hazard ratio 1.50, 95%CI 1.25–1.79, $p < 0.001$) [12].

Notably, however, we observed a significant interaction between pre- and postoperative anaemia status and 1-year mortality in our study, indicating that the development of

Table 4 Multivariable logistic regression model* of postoperative anaemia among patients without pre-operative anaemia.

Variables	Odds ratio	95%CI	p-value
Pre-operative red cell distribution width; %	1.55	1.28–1.89	< 0.001
Cardiopulmonary bypass time; min	1.01	1.00–1.01	0.002
Requirement for intra-operative allogeneic red blood cell transfusion	3.44	1.97–6.03	< 0.001
Sustained postoperative complication	3.06	1.76–5.42	< 0.001

*Multivariable model area under the receiver operating characteristic curve 0.795 (95%CI 0.732–0.858).

new postoperative anaemia had a more pronounced effect on mortality after correcting for several statistically and clinically relevant potential confounders. Several factors could explain this observation. Patients who develop anaemia after surgery may experience greater physiological stress, while those already with pre-operative anaemia may develop compensatory mechanisms through chronic exposure to low haemoglobin, a phenomenon known as `anaemia tolerance´ [31–33]. Moreover, new, persistent anaemia may be a marker of postsurgical complications or a more complicated recovery process.

In the current study, new, persistent postoperative anaemia was associated with elevated pre-operative red blood cell distribution width, longer CPB time, intra-operative transfusion and the occurrence of postoperative complications, findings that are consistent with and expand on previous research [9]. The identified conditions likely impair erythropoiesis through mechanisms involving inflammation and disruption of iron homeostasis [34]. The intriguing association with elevated red blood cell distribution width, a haematologic parameter reflecting impaired erythropoiesis, aligns with previous studies revealing its link to adverse outcome after cardiac surgery [35]. However, specific biological mechanisms connecting red blood cell distribution width to impaired haemoglobin recovery – such as iron deficiency – warrant further investigation. Further investigation is also warranted to elucidate the role of this marker as an indicator of effective haemoglobin regeneration during postoperative recovery. Overall, our study underscores the need for vigilant monitoring of postoperative haemoglobin levels, especially in patients without pre-operative anaemia with complicated surgical and postoperative courses.

Some meta-analyses have suggested that pre-operative intravenous iron therapy may improve mortality outcomes after cardiac surgery [36, 37], although its clinical effectiveness remains a subject of ongoing debate. Given that its haemoglobin-raising effects begin and rise gradually over the 4–8 weeks after treatment [7], its role in enhancing postoperative haemoglobin recovery, rather than solely correcting pre-operative anaemia, warrants further investigation.

This study has several strengths. First, we included a relatively large cohort of patients undergoing valvular heart surgery who received restrictive transfusion with postoperative haemoglobin levels assessed 2 months after discharge, a time point not evaluated commonly in previous studies. Second, by examining both pre-operative and prolonged postoperative anaemia, we provide a more comprehensive understanding of the relationship between peri-operative anaemia and patient outcomes. Third, the analysis was adjusted for a wide range of potential confounders, including postoperative complications, blood transfusion and patient and surgical factors, to better isolate the independent association between anaemia and mortality.

However, this study has some limitations. First, while the observed association between postoperative anaemia and mortality was statistically significant, the retrospective study design precluded definitive conclusions regarding causality. The findings should not be assumed to imply that correcting postoperative anaemia will improve patient survival. Our results are best viewed as hypothesis-generating and highlight the need for prospective studies to clarify whether intervention can modify long-term outcomes. Second, because the study was conducted at a single tertiary centre, the generalisability of the results to other settings may be constrained. Third, although anaemia is a multifactorial condition with distinct aetiologies, we could not assess the underlying causes of pre-operative anaemia systematically. Lastly, the timing and threshold used to define postoperative anaemia were investigator-determined and based on a single haemoglobin measurement, which may not fully reflect the dynamic changes in haemoglobin levels over time. Furthermore, by choosing a common postoperative haemoglobin threshold between the sexes, a sex bias was created. Some recent international consensus statements suggested a uniform threshold of haemoglobin < 130 $g.l^{-1}$ for both sexes [38, 39], along with a recent effort to highlight the importance of sex parity on pre-operative anaemia [40]. However, pre-operative anaemia thresholds for men and women could not be standardised as our analysis using anaemia thresholds at haemoglobin < 130 $g.l^{-1}$ for both sexes would lead to notable reduction in

the non-anaemia–anaemia group (from 2.5% to 1.4%), which would compromise the statistical power of the current study. Finally, by not including patients due to missing haemoglobin values at 2 months after surgery owing to follow-up loss or early death raises the possibility of selection bias.

In conclusion, among patients undergoing valvular heart surgery, anaemia at 2 months postoperatively was an independent risk factor for 1-year mortality in patients with and without pre-operative anaemia. These findings emphasise the importance of postoperative anaemia monitoring and the need for further research to evaluate the effects of enhanced long-term haemoglobin recovery after cardiac surgery.

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References

1. Ranucci M, Baryshnikova E, Castelvecchio S, Pelissero G. Major bleeding, transfusions, and anemia: the deadly triad of cardiac surgery. *Ann Thorac Surg* 2013; **96**: 478–85. https://doi.org/10.1016/j.athoracsur.2013.03.015.
2. Hung M, Besser M, Sharples LD, Nair SK, Klein AA. The prevalence and association with transfusion, intensive care unit stay and mortality of pre-operative anaemia in a cohort of cardiac surgery patients. *Anaesthesia* 2011; **66**: 812–8. https://doi.org/10.1111/j.1365-2044.2011.06819.x.
3. Padmanabhan H, Siau K, Curtis J, Ng A, Menon S, Luckraz H, Brookes MJ. Preoperative anemia and outcomes in cardiovascular surgery: systematic review and meta-analysis. *Ann Thorac Surg* 2019; **108**: 1840–8. https://doi.org/10.1016/j.athoracsur.2019.04.108.
4. Hazen Y, Noordzij PG, Gerritse BM, et al. Preoperative anaemia and outcome after elective cardiac surgery: a dutch national registry analysis. *Br J Anaesth* 2022; **128**: 636–43. https://doi.org/10.1016/j.bja.2021.12.016.
5. Huang J, Firestone S, Moffatt-Bruce S, Tibi P, Shore-Lesserson L. 2021 clinical practice guidelines for anesthesiologists on patient blood management in cardiac surgery. *J Cardiothorac Vasc Anesth* 2021; **35**: 3493–5. https://doi.org/10.1053/j.jvca.2021.09.032.
6. Gómez-Ramirez S, Jericó C, Muñoz M. Perioperative anemia: prevalence, consequences and pathophysiology. *Transfus Apher Sci* 2019; **58**: 369–74. https://doi.org/10.1016/j.transci.2019.06.011.
7. Gómez-Ramírez S, Bisbe E, Shander A, Spahn DR, Muñoz M. Management of perioperative iron deficiency anemia. *Acta Haematol* 2019; **142**: 21–9. https://doi.org/10.1159/000496965.
8. Mazer CD, Whitlock RP, Fergusson DA, et al. Restrictive or liberal red-cell transfusion for cardiac surgery. *N Engl J Med* 2017; **377**: 2133–44. https://doi.org/10.1056/NEJMoa1711818.
9. Li MM, Miles S, Callum J, Lin Y, Karkouti K, Bartoszko J. Postoperative anemia in cardiac surgery patients: a narrative review. *Can J Anaesth* 2024; **71**: 408–21. https://doi.org/10.1007/s12630-023-02650-9.
10. Smoor RM, Rettig TCD, Vernooij LM, et al. Postoperative anaemia and disability-free survival in older cardiac surgery patients. *Br J Anaesth* 2022; **129**: e27–9. https://doi.org/10.1016/j.bja.2022.04.017.
11. Zhou L, Liu X, Yan M, et al. Postoperative nadir hemoglobin and adverse outcomes in patients undergoing on-pump cardiac operation. *Ann Thorac Surg* 2021; **112**: 708–16. https://doi.org/10.1016/j.athoracsur.2021.01.016.
12. Oprea AD, Del Rio JM, Cooter M, et al. Pre- and postoperative anemia, acute kidney injury, and mortality after coronary artery bypass grafting surgery: a retrospective observational study. *Can J Anaesth* 2018; **65**: 46–59. https://doi.org/10.1007/s12630-017-0991-0.
13. Urbanowicz T, Olasińska-Wiśniewska A, Michalak M, et al. The prognostic significance of neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR) and platelet to lymphocyte ratio (PLR) on long-term survival in off-pump coronary artery bypass grafting (OPCAB) procedures. *Biology* 2021; **11**: 11. https://doi.org/10.3390/biology11010034.
14. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol* 2018; **72**: 2231–64. https://doi.org/10.1016/j.jacc.2018.08.1038.
15. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract* 2012; **120**: c179–84. https://doi.org/10.1159/000339789.
16. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* 2001; **286**: 2703–10. https://doi.org/10.1001/jama.286.21.2703.
17. World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. 2011. https://www.who.int/publications/i/item/WHO-NMH-NHD-MNM-11.1 (accessed 31/07/2025).
18. Ranucci M, La Rovere MT, Castelvecchio S, et al. Postoperative anemia and exercise tolerance after cardiac operations in patients without transfusion: what hemoglobin level is acceptable? *Ann Thorac Surg* 2011; **92**: 25–31. https://doi.org/10.1016/j.athoracsur.2011.02.058.
19. Kougias P, Sharath S, Mi Z, Biswas K, Mills JL. Effect of postoperative permissive anemia and cardiovascular risk status on outcomes after major general and vascular surgery operative interventions. *Ann Surg* 2019; **270**: 602–11. https://doi.org/10.1097/sla.0000000000003525.
20. Kougias P, Sharath S, Barshes NR, Chen M, Mills JL Sr. Effect of postoperative anemia and baseline cardiac risk on serious adverse outcomes after major vascular interventions. *J Vasc Surg* 2017; **66**: 1836–43. https://doi.org/10.1016/j.jvs.2017.05.113.

21. Makar T, Hezkial M, Vasudeva M, et al. Associations between postoperative anaemia and unplanned readmission to hospital after major surgery: a retrospective cohort study. *Anaesthesia* 2024; **79**: 839–48. https://doi.org/10.1111/anae.16291.
22. Kolin DA, Lyman S, Della Valle AG, Ast MP, Landy DC, Chalmers BP. Predicting postoperative anemia and blood transfusion following total knee arthroplasty. *J Arthroplast* 2023; **38**: 1262–1266.e2. https://doi.org/10.1016/j.arth.2023.01.018.
23. Giribabu P, Karan N, Sriganesh K, Shukla D, Devi BI. Incidence, risk factors and impact of anemia after elective neurosurgery: a retrospective cohort study. *World Neurosurg X* 2024; **22**: 100289. https://doi.org/10.1016/j.wnsx.2024.100289.
24. Bisbe E. Postoperative anemia: is there a role for iron replacement therapy? *Blood Transfus* 2025; **23**: 42–6. https://doi.org/10.2450/BloodTransfus.906.
25. Benites BD, Magnus MM, Costa L, et al. Consensus of the Brazilian Association of Hematology, Hemotherapy and Cellular Therapy on patient blood management: assessment and management of postoperative anemia. *Hematol Transfus Cell Ther* 2024; **46**(Suppl 1): S72–6. https://doi.org/10.1016/j.htct.2024.02.014.
26. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996; **15**: 361–87.
27. Tibshirani R. Regression shrinkage and selection via the lasso. *J R Stat Soc Series B Stat Methodology* 1996; **58**: 267–88.
28. Therneau TM, Lumley T. Package `survival´. *R Top Doc* 2015; **128**: 28–33.
29. Mathur MB, Ding P, Riddell CA, VanderWeele TJ. Web site and r package for computing e-values. *Epidemiology* 2018; **29**: e45–7. https://doi.org/10.1097/ede.0000000000000864.
30. Ranucci M, Di Dedda U, Castelvecchio S, Menicanti L, Frigiola A, Pelissero G. Impact of preoperative anemia on outcome in adult cardiac surgery: a propensity-matched analysis. *Ann Thorac Surg* 2012; **94**: 1134–41. https://doi.org/10.1016/j.athoracsur.2012.04.042.
31. Totonchi Z, Noohi F, Futuhi F, Azarfarin R, Radbin P. Effects of recombinant erythropoietin on hemoglobin levels and blood transfusion needs in patients with preoperative anemia undergoing cardiac surgery. *Ann Card Anaesth* 2022; **25**: 466–71. https://doi.org/10.4103/aca.aca_42_21.
32. Tankard KA, Park B, Brovman EY, Bader AM, Urman RD. The impact of preoperative intravenous iron therapy on perioperative outcomes in cardiac surgery: a systematic review. *J Hematol* 2020; **9**: 97–108. https://doi.org/10.14740/jh696.
33. Anand IS. Anemia and chronic heart failure implications and treatment options. *J Am Coll Cardiol* 2008; **52**: 501–11. https://doi.org/10.1016/j.jacc.2008.04.044.
34. Singh S, Gudzenko V, Fink MP. Pathophysiology of perioperative anaemia. *Best Pract Res Clin Anaesthesiol* 2012; **26**: 431–9. https://doi.org/10.1016/j.bpa.2012.11.002.
35. Frentiu AA, Mao K, Caruana CB, et al. The prognostic significance of red cell distribution width in cardiac surgery: a systematic review and meta-analysis. *J Cardiothorac Vasc Anesth* 2023; **37**: 471–9. https://doi.org/10.1053/j.jvca.2022.11.015.
36. Liu HM, Tang XS, Yu H, Yu H. The efficacy of intravenous iron for treatment of anemia before cardiac surgery: an updated systematic review and meta-analysis with trial sequential analysis. *J Cardiothorac Surg* 2023; **18**: 16. https://doi.org/10.1186/s13019-023-02119-2.
37. Gupta S, Panchal P, Gilotra K, et al. Intravenous iron therapy for patients with preoperative iron deficiency or anaemia undergoing cardiac surgery reduces blood transfusions: a systematic review and meta-analysis. *Interact Cardiovasc Thorac Surg* 2020; **31**: 141–51. https://doi.org/10.1093/icvts/ivaa094.
38. Shander A, Corwin HL, Meier J, et al. Recommendations from the international consensus conference on anemia management in surgical patients (ICCAMS). *Ann Surg* 2023; **277**: 581–90. https://doi.org/10.1097/sla.0000000000005721.
39. Spahn DR, Muñoz M, Klein AA, Levy JH, Zacharowski K. Patient blood management: effectiveness and future potential. *Anesthesiology* 2020; **133**: 212–22. https://doi.org/10.1097/aln.0000000000003198.
40. Blaudszun G, Munting KE, Butchart A, Gerrard C, Klein AA. The association between borderline pre-operative anaemia in women and outcomes after cardiac surgery: a cohort study. *Anaesthesia* 2018; **73**: 572–8. https://doi.org/10.1111/anae.14185.

Supporting Information

Additional supporting information may be found online via the journal website.

Plain Language Summary.

Appendix S1. Supplemental methods.

Figure S1. Multivariable modelling process for the Cox proportional hazard model.

Figure S2. Multivariable modelling process for the logistic regression model.

Table S1. Comprehensive baseline characteristics and perioperative clinical data of patients according to the four pre- and postoperative anaemia groups.

Table S2. Pre-operative laboratory data of patients according to the four pre-operative and postoperative anaemia groups.

Table S3. Univariable Cox regression results for 1-year mortality.

Table S4. Multivariable Cox proportional hazards model of 1-year mortality with postoperative anaemia as the exposure of interest, stratified by pre-operative anaemia status.

Table S5. Univariable logistic regression results for postoperative anaemia among patients without pre-operative anaemia.